Core Safety Profile

Active substance: Nifedipine CC
Pharmaceutical form(s)/strength: 30 mg, 60 mg, 90 mg and 10 mg, 20 mg, 40 mg Tablets
P-RMS: CZ/H/PSUR/0014/001
Date of FAR: 17.04.2013
4.3 Contraindications

Nifedipine CC must not be used in cases of known hypersensitivity to nifedipine or to any of the excipients.

Nifedipine must not be used in cases of cardiovascular shock.

Nifedipine must not be used in combination with rifampicin because no efficient plasma levels of nifedipine may be obtained due to enzyme induction (see section 4.5).

4.4 Special warnings and precautions for use

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm HG), in cases of manifest heart failure and in the case of severe aortic stenosis.

Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.6).

Nifedipine is not recommended for use during breastfeeding because nifedipine has been reported to be excreted in human milk and the effects of oral absorption of small amounts of nifedipine are not known (see section 4.6).

Careful monitoring of blood pressure must be exercised, also when administered nifedipine with i.v. magnesium sulphate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and foetus.

In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see section 4.5).

Drugs, which are weak to moderate inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are, e.g.:
- macrolide antibiotics (e.g., erythromycin),
- anti-HIV protease inhibitors (e.g., ritonavir),
- azole antimycotics (e.g., ketoconazole),
- the antidepressants nefazodone and fluoxetine,
- quinupristin/dalfopristin,
- valproic acid,
- cimetidine.

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine:
Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see section 4.4).

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

**Rifampicin**
Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see section 4.3).

Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

**Macrolide antibiotics (e.g., erythromycin)**
No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see section 4.4).

Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP3A4 inhibition.

**Anti-HIV protease inhibitors (e.g., ritonavir)**
A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. In addition, drugs of this class have been shown to inhibit in vitro the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded (see section 4.4).

**Azole anti-mycotics (e.g., ketoconazole)**
A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded (see section 4.4).

**Fluoxetine**
A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit in vitro the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see section 4.4).

**Nefazodone**
A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see section 4.4).

**Quinupristin / Dalfopristin**
Simultaneous administration of quinupristin / dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine (see section 4.4).

**Valproic acid**
No formal studies have been performed to investigate the potential interaction between nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded (see section 4.4).

**Cimetidine**
Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect (see section 4.4).

**Further studies**

**Cisapride**
Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

**Cytochrome P450 3A4 system inducing anti-epileptic drugs, such as phenytoin, carbamazepine and phenobarbitone**
Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an increase of the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment with phenytoin is discontinued.

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy cannot be excluded.

**Effects of nifedipine on other drugs:**

**Blood pressure lowering drugs**
Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives, such as:
- diuretics,
- β-blockers,
- ACE-inhibitors,
- AT-1 antagonists,
- other calcium antagonists,
- α-adrenergic blocking agents,
- PDE5 inhibitors,
- α-methyldopa.
When nifedipine is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

**Digoxin**
The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in plasma concentrations of digoxin. The patient should therefore be checked for symptoms of digoxin overdosage as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

**Quinidine**
When nifedipine and quinidine have been administered simultaneously, lowered quinidine or, after discontinuation of nifedipine, a distinct increase in plasma concentrations of quinidine has been observed in individual cases. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose are recommended. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine. Therefore, the blood pressure should be carefully monitored, if quinidine is added to an existing therapy with nifedipine. If necessary, the dose of nifedipine should be decreased.

**Tacrolimus**
Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Data recently published indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

**Drug-food interactions:**
**Grapefruit juice**
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice this effect may last for at least 3 days after the last ingestion of grapefruit juice.
Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nifedipine.

**Other forms of interaction:**
Nifedipine may cause falsely increased spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is unaffected.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**
Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.4).

There are no adequate and well controlled studies in pregnant women. The available information is inadequate to rule out adverse drug effects on the unborn and newborn child.
In animal studies nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity.

From the clinical evidence available a specific prenatal risk has not been identified. Although an increase in perinatal asphyxia, caesarean delivery as well as prematurity and intrauterine growth retardation has been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect.

**Breast-feeding**

Nifedipine is excreted in the breast milk. The nifedipine concentration in the milk is almost comparable with mother serum concentration. For immediate release formulations, it is proposed to delay breastfeeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant (see section 4.4).

**Fertility**

In single cases of *in-vitro* fertilization calcium-antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in-vitro* fertilization, and where no other explanation can be found, calcium-antagonists like nifedipine should be considered as possible causes.

4.7 **Effects on ability to drive and use machines**

Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

4.8 **Undesirable effects**

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

The frequencies of ADRs reported with nifedipine are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing postmarketing surveillance, and for which a frequency could not be estimated, are listed under "Not known".
<table>
<thead>
<tr>
<th>System Organ Class (MedDRA)</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Agranulocytosis</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reaction</td>
<td>Allergic oedema / angioedema (incl. larynx oedema)</td>
<td>Pruritus Urticaria Rash</td>
<td>Anaphylactic/ anaphylactoid reaction</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Anxiety reactions</td>
<td>Sleep disorders</td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>Hyperglycaemia</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Vertigo</td>
<td>Par-/Dysaesthesia</td>
<td>Hypoaesthesia Somnolence</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>Palpitations</td>
<td>Chest Pain (Angina Pectoris)</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>Oedema</td>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Nosebleed</td>
<td>Nasal congestion</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
<td>Gastrointestinal and abdominal pain</td>
<td>Gingival hyperplasia</td>
<td>Vomiting Gastrooesophageal sphincter insufficiency</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Transient increase in liver enzymes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema</td>
<td></td>
<td>Toxic Epidermal Necrolysis</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle cramps</td>
<td>Joint swelling</td>
<td>Arthralgia</td>
<td></td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>System Organ Class (MedDRA)</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal and urinary disorders</td>
<td>Polyuria</td>
<td>Dysuria</td>
<td></td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Erectile dysfunction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Feeling unwell</td>
<td>Unspecific pain</td>
<td>Chills</td>
<td></td>
</tr>
</tbody>
</table>

*= may result in life-threatening outcome.*

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

4.9 Overdose

Symptoms
The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardiac / bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Management of Overdose
As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority.

After oral ingestion thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine.

Particularly in cases of intoxication with slow-release products like nifedipine CC elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Haemodialysis serves no purpose, as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Bradycardiac heart rhythm disturbances may be treated symptomatically with β-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10 - 20 ml of a 10 % calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs is determined solely by the effect obtained.
Additional liquid or volume must be administered with caution because of the danger of overloading the heart.